

WHAT IS CLAIMED IS;

1. A process for producing one or more human monoclonal antibodies which bind specifically to Shiga toxin or Shiga-like toxin, which comprises the following steps:

(1) administering Shiga-like toxoid I or Shiga-like toxoid II as an antigen to a transgenic mouse having human genes and inducing an immune response in the transgenic mouse;

(2) isolating splenocytes from the transgenic mouse following an immune response by the transgenic mouse and fusing the splenocytes to mouse myeloma cells to obtain mouse hybridomas producing human monoclonal antibodies; and

(3) screening the human monoclonal antibodies to obtain the human monoclonal antibodies which bind specifically to Shiga toxin or Shiga-like toxin.

2. The process for producing one or more human monoclonal antibodies defined in claim 1 wherein the human monoclonal antibodies which bind specifically to Shiga toxin or Shiga-like toxin bind to Shiga-like toxin I.

3. The process for producing one or more human monoclonal antibodies defined in claim 1 wherein the human monoclonal antibodies which bind specifically to Shiga toxin or Shiga-like toxin bind to Shiga-like toxin II.

1           4.    The process for producing one or more human  
2 monoclonal antibodies defined in claim 1 wherein the human  
3 monoclonal antibodies which bind specifically to Shiga toxin or  
4 Shiga-like toxin bind to Shiga toxin.

1           5.    The process for producing one or more human  
2 monoclonal antibodies defined in claim 1 wherein according to step  
3 (1) the transgenic mouse having human genes is capable of  
4 expressing a diversity of human heavy and light chain  
5 immunoglobulins.

1           6.    The process for producing one or more human  
2 monoclonal antibodies defined in claim 1 wherein according to step  
3 (1) the transgenic mouse having human genes is capable of  
4 expressing unrearranged human heavy and light chain  
5 immunoglobulins.

1           7.    The process for producing one or more human  
2 monoclonal antibodies defined in claim 1 wherein according to step  
3 (1) the Shiga-like toxoid I or Shiga-like toxoid II antigen is  
4 intraperitoneally administered in an amount of 20 to 100  $\mu$ g on day  
5 1 to the transgenic mouse in complete Freund's adjuvant followed by  
6 weekly intraperitoneal immunizations with 5 to 20  $\mu$ g of antigen in  
7 incomplete Freund's adjuvant.

1           8. A human monoclonal antibody which binds specifically  
2       to Shiga toxin or Shiga-like toxin prepared by the process defined  
3       in claim 1.

1           9. The human monoclonal antibody defined in claim 8 that  
2 specifically binds to Shiga-like toxin II as the Shiga-like toxin.

10. The human monoclonal antibody defined in claim 9 that specifically binds to the A-subunit of Shiga like toxin II.

11. The human monoclonal antibody defined in claim 9 that specifically binds to the A-subunit of Shiga like toxin II and that neutralizes multiple variants of Shiga likme toxin II.

12. The human monoclonal antibody defined in claim 8 that specifically binds to various clinical variants of Shiga-like toxin II as the Shiga-like toxin.

1           13. The human monoclonal antibody defined in claim 9  
2           that specifically binds to Shiga-like toxin II and which is  
3           selected from the group consisting of 5C12 and 3E9.

1           14. The human monoclonal antibody defined in claim 8  
2   that specifically binds to Shiga-like toxin I as the Shiga-like  
3   toxin.

4           15. The human monoclonal antibody defined in claim 8  
5 that specifically binds to various clinical variants of Shiga-like  
6 toxin I as the Shiga-like toxin.

1           16. The human monoclonal antibody defined in claim 8  
2 that will not elicit reaction in humans to foreign proteins.

3           17. A therapeutic method of treating an individual for  
4 hemolytic uremic syndrome or of protecting an individual against  
5 hemolytic uremic syndrome, said method comprising the steps of:  
6

7           (a) producing one or more human monoclonal antibodies  
8 which bind specifically to Shiga toxin or Shiga-like toxin, said  
9 human monoclonal antibodies which bind specifically to Shiga toxin  
10 or Shiga-like toxin obtained by the following steps:

11           (1) administering Shiga-like toxoid I or Shiga-  
12 like toxoid II as an antigen to a transgenic mouse having human  
13 genes and inducing an immune response in the transgenic mouse;

14           (2) isolating splenocytes from the transgenic  
15 mouse following an immune response by the transgenic mouse and  
16 fusing the splenocytes to mouse myeloma cells to obtain mouse  
17 hybridomas producing human monoclonal antibodies; and

          (3) screening the human monoclonal antibodies  
to obtain the human monoclonal antibodies which bind specifically  
to Shiga toxin or Shiga-like toxin; and

18 (b) administering the human monoclonal antibodies which  
19 bind specifically to Shiga toxin or Shiga-like toxin to the  
20 individual in a therapeutically effective amount.

1 18. The therapeutic method defined in claim 17 wherein  
2 the human monoclonal antibodies which bind specifically to Shiga  
3 toxin or Shiga-like toxin bind to Shiga-like toxin I.

1 19. The therapeutic method defined in claim 18 wherein  
2 the human monoclonal antibodies which bind specifically to Shiga  
3 toxin or Shiga-like toxin bind to Shiga-like toxin II.

1 20. The therapeutic method defined in claim 18 wherein  
2 the human monoclonal antibodies which bind specifically to Shiga  
3 toxin or Shiga-like toxin bind to Shiga toxin.

1 21. The therapeutic method defined in claim 17 wherein  
2 the hemolytic uremic syndrome is caused by a Shiga-like toxin  
3 producing bacteria.

1 22. The therapeutic method defined in claim 21 wherein  
2 the Shiga-like toxin producing bacteria is Enterohemorrhagic  
3 Escherichia coli.

1           23. The therapeutic method defined in claim 17 wherein  
2 the individual is protected from hemolytic uremic syndrome through  
3 passive immunization by administering to the individual a  
4 prophylactically effective amount of the human monoclonal  
5 antibodies which bind specifically to Shiga toxin or Shiga like  
6 toxin.

1           24. The therapeutic method defined in claim 19 wherein  
2 the human monoclonal antibodies which bind specifically to Shiga  
3 like toxin II specifically bind to the A-subunit of Shiga like  
4 toxin II.

1           25. The therapeutic method defined in claim 19 wherein  
2 the human monoclonal antibodies which bind specifically to Shiga  
3 like toxin II specifically bind to the A-subunit of Shiga like  
4 toxin II and neutralize multiple variants of Shiga like toxin II.